POST-ORLANDO 2025
Novità dal Meeting della Società Americana di Ematologia

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Torino
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UNIVERSITÀ DI ROMA

Leucemie acute linfoidi

DICHIARAZIONE

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Amgen					X	X	
Incyte					X	**X**	
Gilead						**X**	
Pfizer					X	X	

Topics

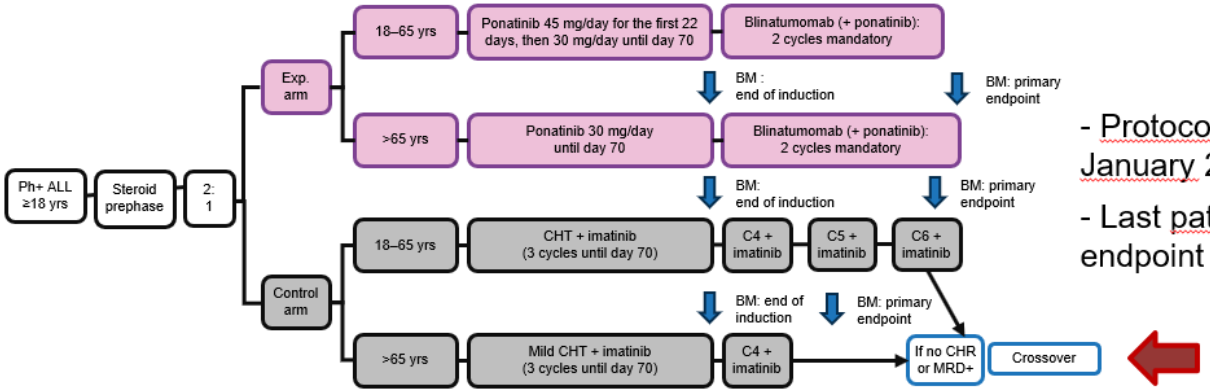
- **Ph +ALL**
  - Abstract N 439: GIMEMA ALL 2820 for newly diagnosed Ph+ ALL study. *Chiaretti S, et al.*
  - Abstract N 441: Dasa+ ino for newly diagnosed Ph+ ALL study *Patel AA, et al.*

- **Ph-ALL**

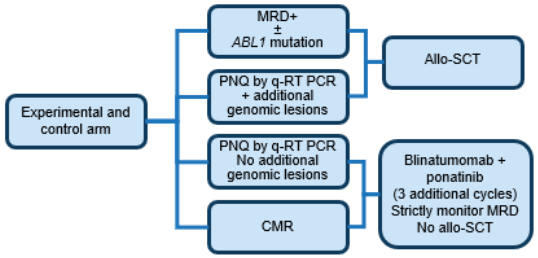
  - Abstract N 643: Quest trial: final results, *Boissel et al*
  - Abstract N 645: Ven+ ino in R/R patients, *Luskin et al*
  - Abstract 647: MK1045 in R/R ALL *Wang Y, et al.*

GIMEMA ALL2820 Phase III Trial

Frontline treatment of adult Ph+ ALL (≥18 years, no upper age limit) with ponatinib plus steroids followed by blinatumomab compared to chemotherapy with imatinib



- Protocol closed to enrolment in January 2025.
- Last patient reached primary endpoint in June 2025.



- CNS prophylaxis strengthened:
15 triple medicated lumbar punctures
18 if CNS+ at diagnosis.

Chiaretti et al, Abs 439

GIMEMA ALL2820. Patients' features (n=236)

	Experimental arm N=158	Control arm N=78
Age, median (range)	56.5 (19-84)	55 (21-79)
>65 years (%)	44 (28)	21 (27)
Gender: M/F (%)	79/79 (50/50)	48/31(59/41)
WBC x10^9/l, median (range)	10.5 (0.1-244)	13.4 (0.7-231)
≥30x10^9/l (%)	43 (27)	27 (31)
≥70x10^9/l (%)	16 (10)	7 (9.3)
CNS+	15 (9.9)	11(15)
p190 (%)	111 (70)	49 (64)
p210, p190/210 (%)	41 (26), 6 (4)	24 (31.7), 4 (5.2)
IKZF1^{plus} (%)	52 (34)	19 (26)

Chiaretti et al, Abs 439

GIMEMA ALL2820. Hematologic responses

End of induction (d +70)	Experimental arm (n=158)	Control arm (n=78)	p
CHR	149 **(94.3%)**	62 **(79.4%)**	**0.004**
Deaths	4 **(2.5%)**	8 **(10.2%)**	
Refractory	-	1 **(1.3%)**	
Off-treatment	5 **(2.8%)**	7 **(8.9%)**	

GIMEMA ALL2820. Molecular responses by ITT

Experimenal arm (n=158)	No molecular responses (%)	CMR	PNQ	Overall molecular responses (%)	D-ALBA (n=63):	Overall molecular responses (%)
End of induction	84 (53.2)	48 (30.4)	26 (16.5)	**74 (46.8)**	End of induction	**17 (26.9)**
After 2 blina cycles	46 (29.1)	82 (51.9)	30 (19)	**112 (70.9)**	After 2 blina cycles	**33 (52.4)**
Control arm (n=78)						
End of induction	44 (56.4)	28 (35.9)	6 (7.7)	**34 (43.6)**		
After 4/6 CHT cycles*	40 (51.3)	29 (37.2)	9 (11.5)	**38 (48.7)**		

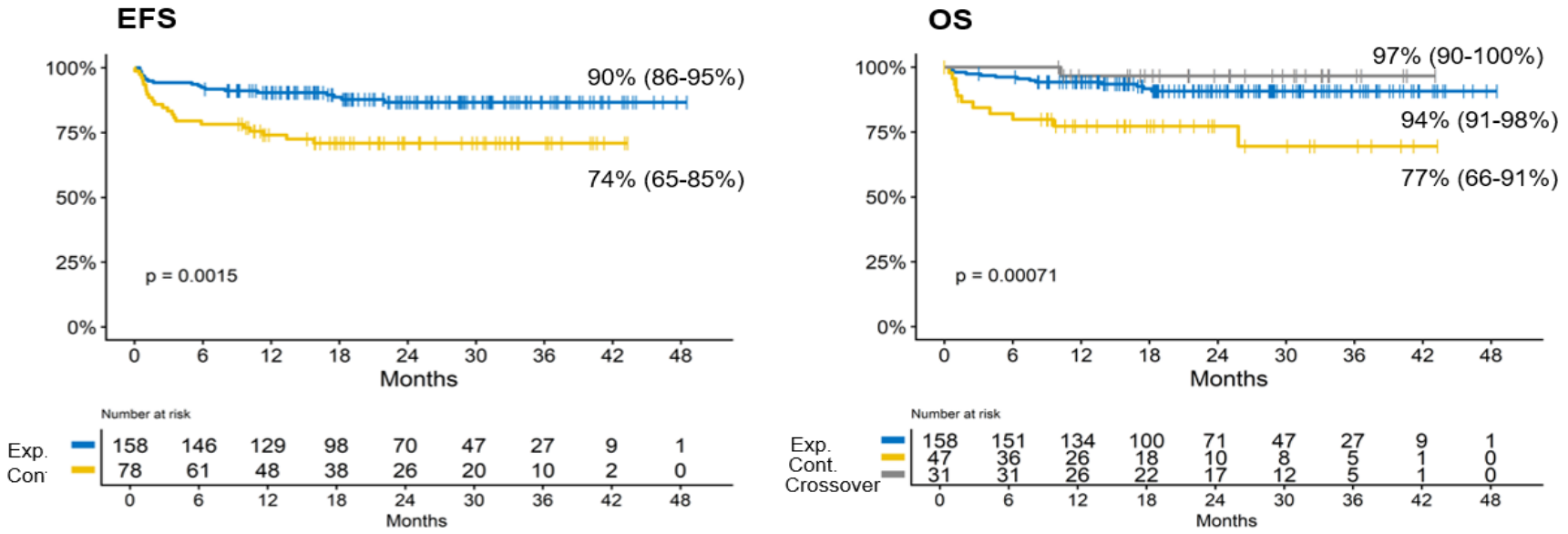
***p*= ns**

***p*= <0.001**

*Depending on age

Chiaretti et al, Abs 439

GIMEMA ALL2820. EFS and OS



Median follow-up: 23.4 months (0.1- 48.5)

Chiaretti et al, Abs 439

GIMEMA ALL2820. Conclusions

- The first results of the phase III GIMEMA ALL2820 trial show for the first time, in a head-to-head comparison, a significant advantage of a chemo-free, targeted/immunotherapeutic based approach over a TKI/chemotherapy strategy, with higher CHR and MRD responses, fewer deaths and improved EFS and OS.
- An increase in MRD negativity and less relapses have so far been observed compared to the D-ALBA trial.
- A crossover is capable of rescuing MRD+ patients in the control arm.
- A biology-driven transplant allocation strategy appears to be feasible and effective.

- A chemo-free approach should be the new standard for adult Ph+ ALL.

Ongoing

- *BCR::ABL1* and IG/TR MRD monitoring by RQ-PCR and ddPCR (NGS in a subset).
- Monitoring of *ABL1* mutations by ddPCR in MRD+ patients.
- Host immune modulation *(Ansuinelli M et al, Leukemia in press).*
- Quality of life.

Chiaretti et al, Abs 439

Primary efficacy analysis of phase II study investigating tyrosine kinase inhibitor (TKI) and inotuzumab ozogamicin-based therapy for newly diagnosed Philadelphia-chromosome positive acute lymphoblastic leukemia (Ph+ ALL)

Anand A. Patel, Adam S. DuVall, Caner Saygin, Howard Weiner, Emily Dworkin, Afsheen Noorani, Jamie Mathews, Angela Lager, Sandeep Gurbuxani, Peng Wang, Rafael Madero-Marroquin, Austin Wesevich, Gregory W. Roloff, Mariam T. Nawas, Michael W. Drazer, Satyajit Kosuri, Michael Thirman, Richard A. Larson, Olatoyosi Odenike, Theodore Karrison, Wendy Stock

Initial Treatment Schema (1) : InO + TKI

Course 1:
28 days

Dasatinib
140 mg daily

Dexamethasone
10 mg/m² days 1-7; 15-22

InO
0.8 mg/m² day 8
0.5 mg/m² day 15
0.5 mg/m² day 22

Course 2:
28 days

Dasatinib
140 mg daily

InO
0.5 mg/m² day 1
0.5 mg/m² day 8
0.5 mg/m² day 15

MR4 or better

Course 3:
84 days

Dasatinib
140 mg daily

POMP*

Course 4:
28 days

Dasatinib
140 mg daily

InO
0.5 mg/m²
Day 1 and 15

Course 5:**
84 days

Dasatinib
140 mg daily

POMP*

MR3 or worse

Ponatinib
30 mg daily

POMP*

Ponatinib
30 mg daily

InO
0.5 mg/m²
Day 1 and 15

Ponatinib
30 mg daily

POMP*

If worse than MR4, OFF PROTOCOL

15 IT Chemo given over the course of protocol
Post Course 5 therapy – continue daily TKI
*POMP – Prednisone, Vincristine, 6-MP, MTX
**Course 5 is administered 3 times

Primary Endpoint: Rate of MR3 (≤0.1% by *BCR::ABL1* PCR) or better after 2 courses of therapy

Patel AA, et al. Abs N 441

Revised Treatment Schema (2) : InO + TKI

Course 1:
28 days

Dasatinib
140 mg daily

Dexamethasone
10 mg/m^2 days 1-7; 15-22

Course 2:
28 days

InO
0.5 mg/m^2 day 1
0.5 mg/m^2 day 8
0.5 mg/m^2 day 15

MR4 or better

Course 3:
84 days

Dasatinib
100 mg daily

POMP*

Course 4:
28 days

Dasatinib
100 mg daily

Course 5:**
84 days

Dasatinib
100 mg daily

POMP*

MR3 or worse

Ponatinib
30 mg daily

POMP*

Ponatinib
30 mg daily

If <MR4 add:
InO
0.5 mg/m^2 day 1
0.5 mg/m^2 day 15

Ponatinib
30 mg daily

POMP*

If worse than MR4, OFF PROTOCOL

15 IT Chemo given over the course of protocol
Post Course 5 therapy – continue daily TKI
*POMP – Prednisone, Vincristine, 6-MP, MTX
**Course 5 is administered 3 times

Patient Characteristics (N=21)

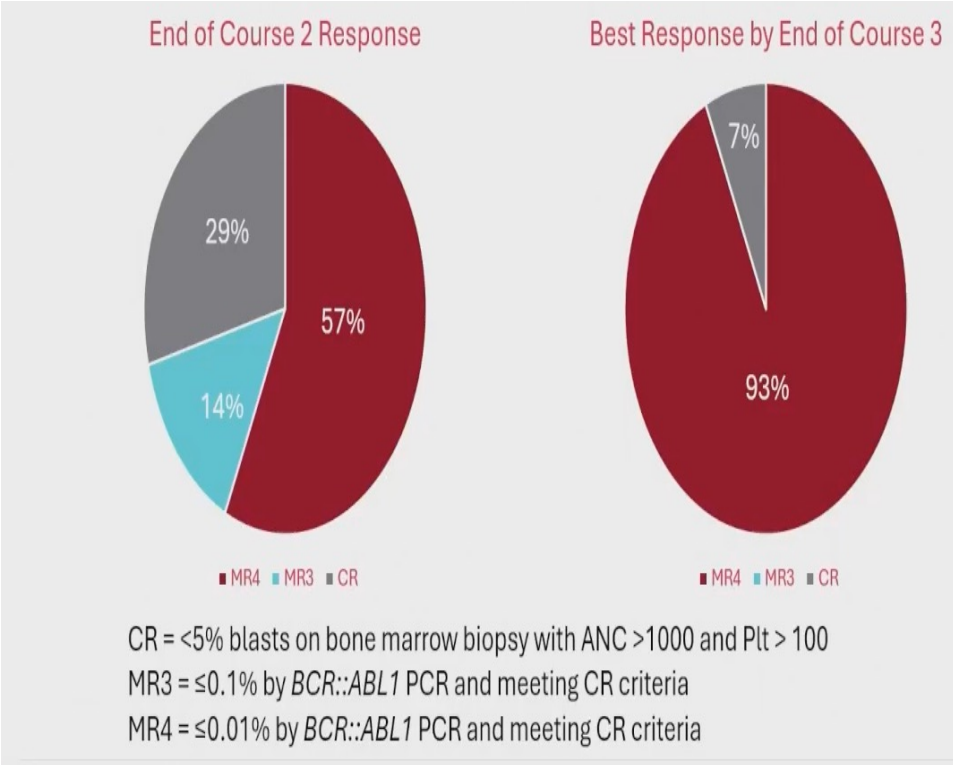
Demographics	
Median Age (range)	60 (21-79)
Female	57%
Race/Ethnicity	
Non-Hispanic White	53%
Non-Hispanic Black	24%
Hispanic	14%
Not Reported	10%
***BCR::ABL1* Transcript**	
p190	67%
p210	29%
atypical	5%

Laboratory Values at Diagnosis	
WBC (10^3/μL), median (range)	12.3 (1.2-149.2)
WBC ≥ 70K/μL	19%
Platelet Count (10^3/μL), median (range)	34 (12-224)
Hemoglobin (g/dL), median (range)	8 (5.9-12.6)
% CD22 expression on blasts, median (range)	93 (33-99)
Molecular Aberrations	
IKZF1 aberration	38%
IKZF1^{plus*}	14%

*defined per Foa et al, NEJM 2020

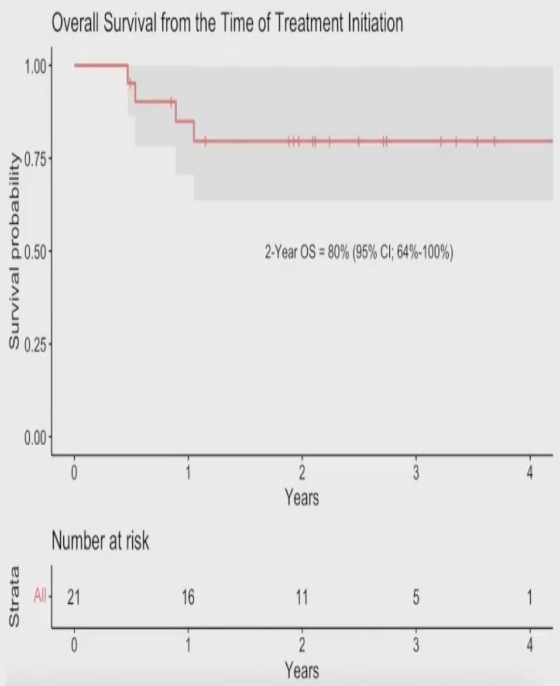
Patel AA, et al. Abs N 441

Molecular response



CR = <5% blasts on bone marrow biopsy with ANC >1000 and Plt > 100
MR3 = ≤0.1% by *BCR::ABL1* PCR and meeting CR criteria
MR4 = ≤0.01% by *BCR::ABL1* PCR and meeting CR criteria

OS



Total Cohort (21 patients)

- Median follow-up 2.1 years
- **0 patients received allogeneic transplant**
- **0 CNS relapses**
- 1 post-protocol systemic relapse
  - Features at diagnosis: p190, WBC≥70K, *IKZF1*m
  - Features at relapse: *IKZF1*m, *ABL1* T315I
- 4 deaths (3 off-protocol, 1 on protocol)
  - 2 due to sepsis
  - 1 due to GI bleed
  - On-protocol death during Course 5 (respiratory failure due to pneumonia and COPD)

Patel AA, et al. Abs N 441

Toxicity Profile – Grade 3+ Events

Adverse Event	Incidence*
Anemia	19%
COVID-19	19%
Dyspnea	19%
Pneumonia	19%
Fatigue	14%
GI Bleed	14%
Nausea/vomiting	14%
Thrombocytopenia	14%

Adverse Event	Incidence*
Abdominal Pain	10%
Anorexia	10%
Bacteremia	10%
Elevated Transaminase	10%
Encephalopathy	10%
Fever	10%
Intracranial hemorrhage	10%

Adverse Event	Incidence*
Muscle Weakness	10%
Neutropenic Fever	10%
Neutropenia	10%
Pancreatitis	10%
Respiratory Failure	10%
Upper Respiratory Infection	10%
Veno-Occlusive Disease**	10%

***Grade 3+ events noted in ≥2 patients are listed**

**VOD occurred 9 days after Course I and 24 days after Course II, both patients treated on Schema 1

Patel AA, et al. Abs N 441

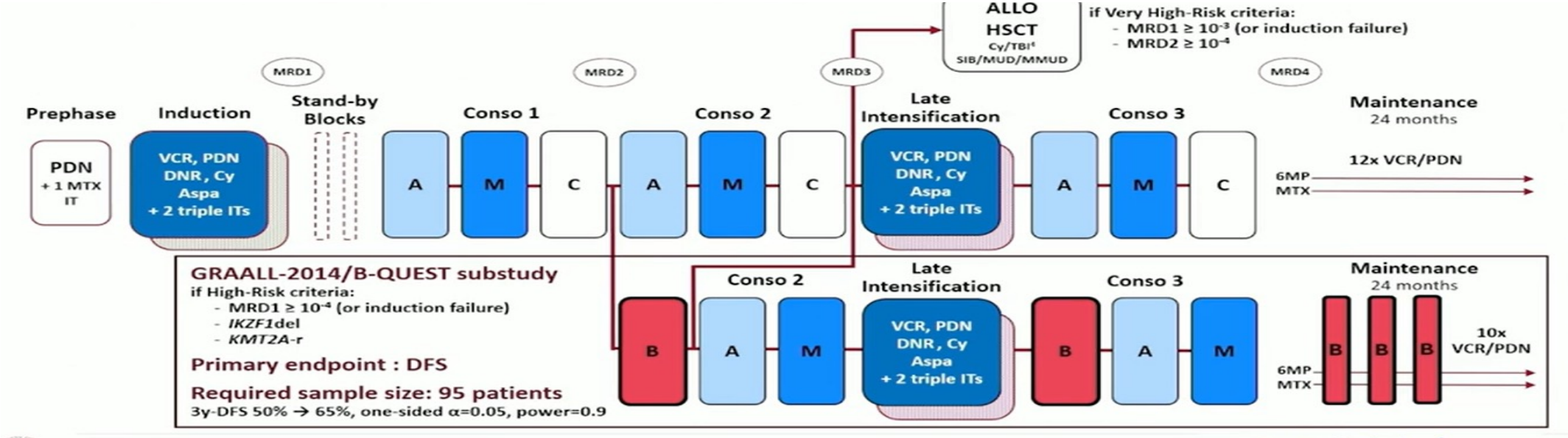
Conclusions

- Dasatinib + InO-based induction has high rates of ≥MR3 after 2 courses of therapy
- VOD was noted in 2 of 7 patients treated with Schema 1; **no VOD has been observed in patients treated with Schema 2**
- Transitioning patients from dasatinib to ponatinib if a MR4 is not achieved after 2 courses leads to deepening of response
- **All patients treated have achieved either MR4 or MRD- by NGS by the end of Course 3**
- **76% EFS with median follow-up of 2.1 years; there have been 0 CNS relapses and no patients have received allo-HCT**
- This is a highly effective regimen with efficacy/safety similar to TKI + blinatumomab based approaches

Patel AA, et al. Abs N 441

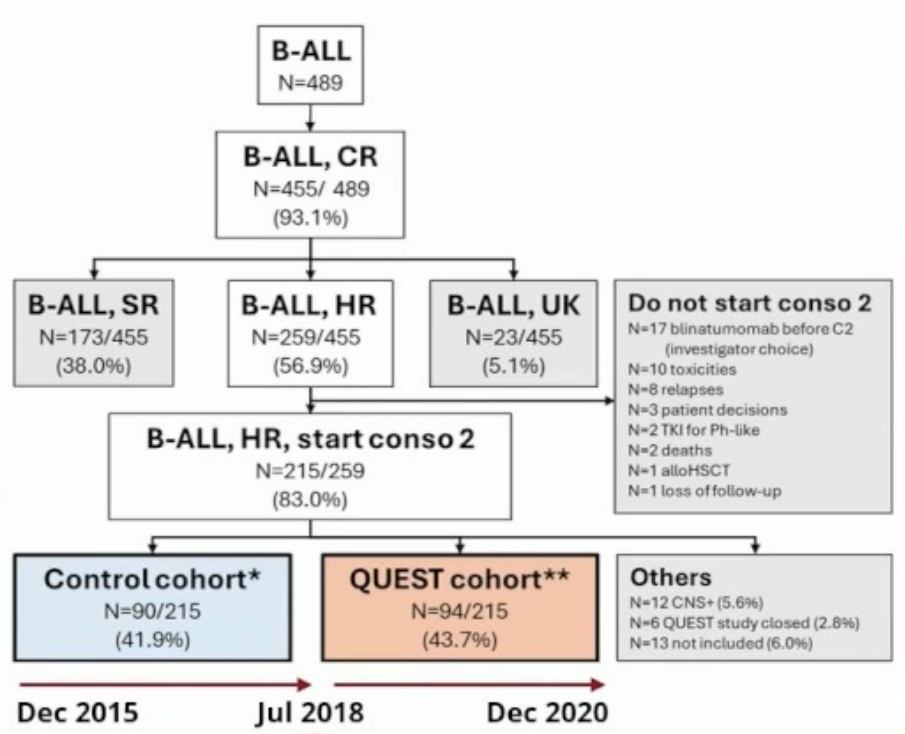
Blinatumomab Consolidation in High-risk Philadelphia Chromosome-negative B-cell Acute Lymphoblastic Leukemia in Adults: Final Report of the GRAALL-2014/B-QUEST Study

Nicolas Boissel, Françoise Huguet, Thibaut Leguay, Mathilde Hunault, Rathana Kim, Yosr Hicheri, Marie Passet, Patrice Chevallier, Marie Balsat, Cédric Pastoret, Eric Delabesse, Sébastien Maury, Anne Thiebaut, Florence van Obbergh, Thomas Cluzeau, Martine Escoffre-Barbe, Nicole Straetmans, Johanna Konopacki, Amine Belhabri, Alban Villate, Florence Pasquier, Ioana Vaida, Laurence Sanhes, Sabine Blum, Magda Alexis, Mathilde Lamarque, Laure Farnault, Céline Berthon, Véronique Lhéritier, Norbert Ifrah, Carlos Graux, Yves Chalandon, Emmanuelle Clappier, Hervé Dombret



Boissel N, et al. Abs N 643

Patients' flow and features



	QUEST N=94	Control N=90	p
Median age (y), range	34 (18-59)	35 (18-59)	0.82
Male/Female	51/43	40/50	0.19
Median WBC (x10⁹/L), range	12 (1-449)	7 (0-637)	0.36
Genetics (N), %			
KMT2A-r*	16/94 (17)	21/90 (23)	0.36
Ph-like	17/94 (18)	16/90 (18)	1.00
*IKZF1*del*	37/93 (40)	32/88 (36)	0.65
Early outcome **			
CR (N), %	94 (100)	90 (100)	1.00
CR after salvage (N), %	5 (5)	8 (9)	0.40
MRD1 ≥ 10^{-4}* (N), %	68/93 (73)	70/87 (80)	0.29
MRD2 ≥ 10^{-4} (N), %	41/92 (45)	33/84 (39)	0.54

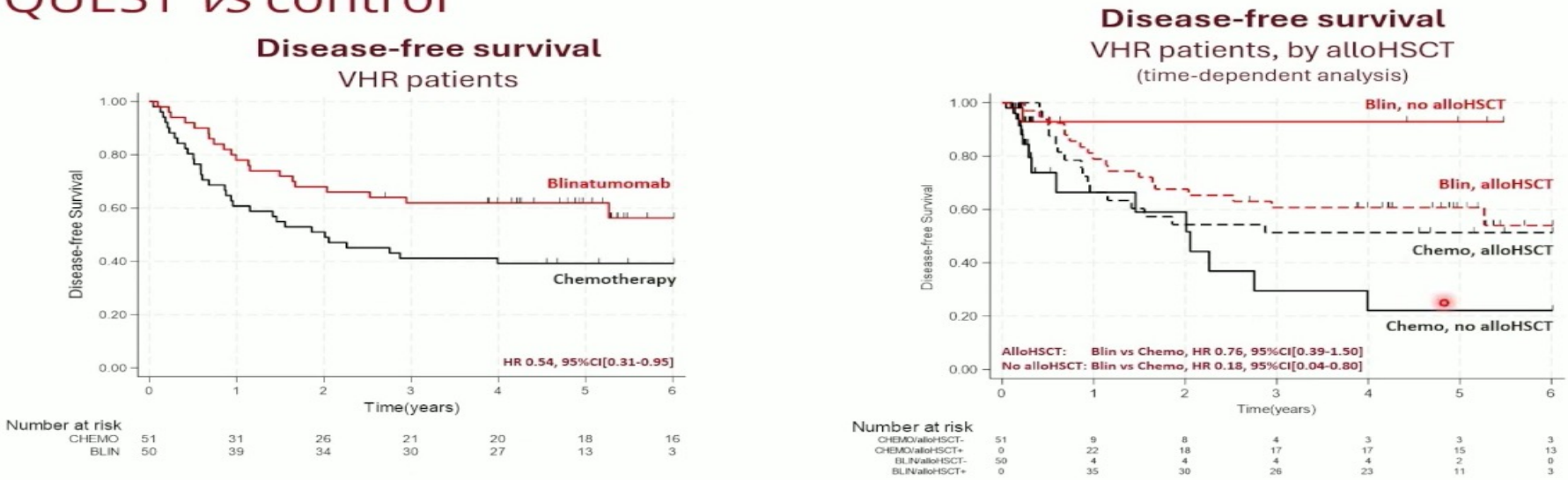
*Criteria for high-risk stratification
**Before inclusion in QUEST

Boissel N, et al. Abs N 643

Consolidation with blinaumomab was beneficial to all subsets

Patients eligible to alloHSCT (VHR)

QUEST *vs* control



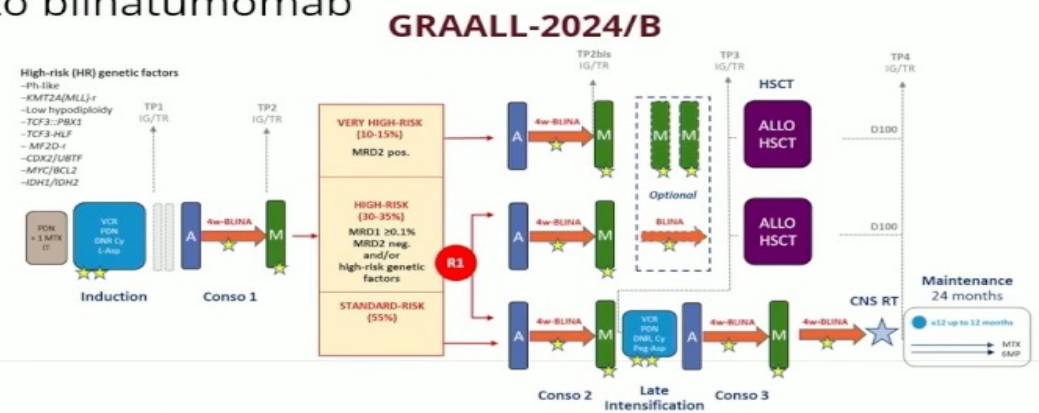
- The benefit of prior blinatumomab in patients who ultimately underwent transplantation was limited
- Despite low numbers, VHR patients who could not be bridged to alloHSCT showed a marked benefit from blinatumomab

Boissel N, et al. Abs N 643

Blinatumomab in consolidation for HR B-ALL

Conclusion

- Blinatumomab in consolidation for HR Ph-negative B-ALL improves MRD response and patient outcome
- This benefit is consistently observed among patient subgroup (age, WBC, Ph-like...)
- The study does not demonstrate an additional benefit of bridging to alloHSCT in patients with poor MRD response and prior exposure to blinatumomab
- In the GRAALL-2024 high-risk patients (poor oncogenetics and/or MRD1) who achieved a undetectable MRD response after binatumomab are randomized to receive alloHSCT or not



Boissel N, et al. Abs N 643

Venetoclax plus Inotuzumab Ozogamicin for Relapsed and Refractory ALL: Results of a Phase I Trial

Marlise R. Luskin[1], Julia Keating[2], Benjamin Frost[3], Yael Flamand[2], Jacqueline S. Garcia[1], Richard M. Stone[1], Rebecca Leonard[1], Stella L. Jaeckle[1], Chase M. Weizer[1], Jessica Lee[1], Jeremy Ryan[1], Ilene Galinsky[1], Evan C. Chen[1], Eric S. Winer[1], Anthony Letai[1], Mark. A. Murakami[1], Daniel J. DeAngelo[1]

Patients

Dose escalation:
DL1: 3 patients
DL2: 6 patients

Dose expansion:
14 patients

Venetoclax
200 mg (DL1)
400 mg (DL2)

	Dose Escalation (n = 9)	Dose Expansion (n = 14)	Overall (N = 23)
Age, median (min, max)	45 (25, 74)	38.5 (24, 73)	39 (24, 74)
Sex, n (%)			
Female	5 (55.6%)	6 (42.9%)	11 (47.8%)
Race/ethnicity, n (%)			
White, non-Hispanic	6 (66.7%)	8 (57.1%)	14 (60.9%)
Hispanic	2 (22.2%)	4 (28.6%)	6 (26.1%)
Other	1 (11.1%)	2 (14.3%)	3 (13.0%)
Disease type, n (%)			
ALL	7 (77.8%)	8 (57.1%)	15 (65.2%)
LBL	2 (22.2%)	6 (42.9%)	8 (34.8%)
Philadelphia chromosome, n (%)			
Negative	7 (77.8%)	12 (85.7%)	19 (82.6%)
Positive	2 (22.2%)	2 (14.3%)	4 (17.4%)
Prior lines of treatment			
1	4 (44.4%)	7 (50.0%)	11 (47.8%)
2	5 (55.6%)	5 (35.7%)	10 (43.5%)
3	0	2 (14.3%)	2 (8.7%)
Prior HSCT			
Yes	3 (33.3%)	2 (14.3%)	5 (21.7%)
CNS involvement, n (%)			
No	8 (88.9%)	13 (92.9%)	21 (91.3%)
Yes	1 (11.1%)	0	1 (4.3%)
Unknown	0	1 (7.1%)	1 (4.3%)

Luskin M, et al. Abs N 645

Grade ≥ 3 Toxicities *Treatment Emergent*

Toxicity	N	%
Hematologic		
Thrombocytopenia	10	43.5
Leukopenia	9	39.1
Neutropenia	9	39.1
Anemia	2	8.7
Leukocytosis	1	4.3
Infectious		
Febrile neutropenia	2	8.7
Viral pneumonia	1	4.3
Hepatobiliary and gastrointestinal		
Hepatic dysfunction	1	4.3
Portal hypertension	1	4.3
Metabolism and nutrition disorders		
Failure to thrive	1	4.3
Nervous system disorders		
Altered mental status	1	4.3
Vascular disorders		
Hypotension	1	4.3

- No early mortality
- Most common grade ≥3 toxicities were hematologic
- Febrile neutropenia: n=2 (8.7%)
  - No sepsis or ICU admission
- Sinusoidal obstructive syndrome (SOS)
  - n=4, all post-protocol, 3 after HSCT
  - Post-HSCT SOS rate: 20% (3/15)
    - All treated with defibrotide
    - 1 fatal case in a 2nd transplant
  - One case of non-SOS liver toxicity with ascites during protocol therapy

Luskin M, et al. Abs N 645

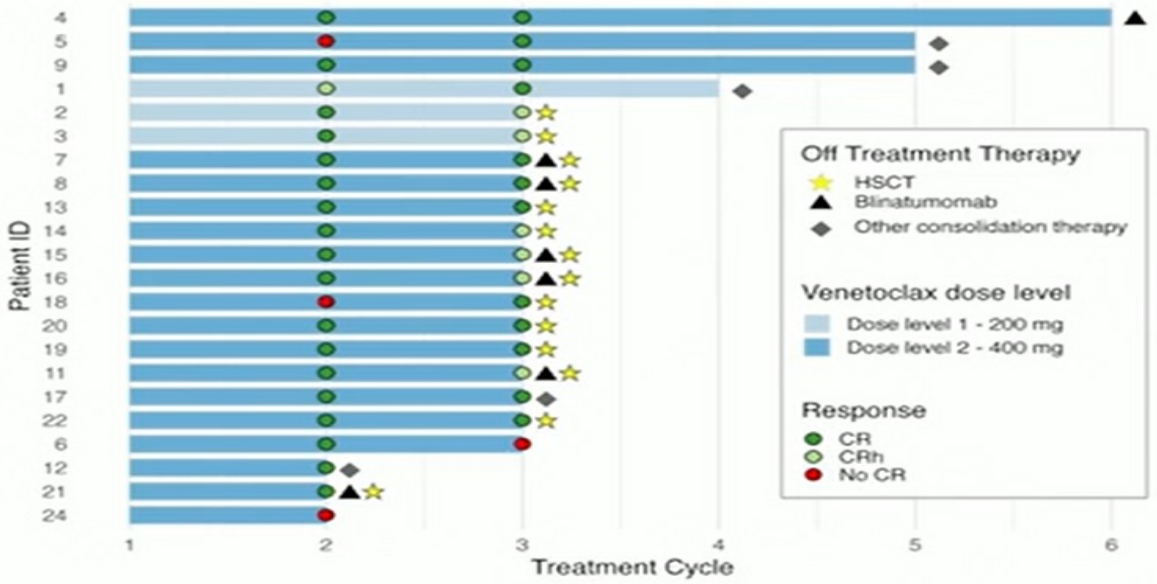
CR rate:95.5%;

MRD- for flow: 89.9%;

MRD- for NGS:73.3%

Median follow-up: 19.6 months

- **Median cycles: 2 (range 1-5)**
  - 1 cycle: 4 patients (17.4%)
  - 2 cycles: 15 patients (65.2%)
  - ≥3 cycles: 4 patients (17.4%)
- **Patient disposition**
  - HSCT: 15 (68.2%)
    - Blinatumomab bridge: 6
  - Other consolidation: 5 (22.7%)
  - Treatment failure:
    - 1 (4.5%) refractory
    - 1 (4.5%) early relapse



Luskin M, et al. Abs N 645

Updated Results From the Phase 1b/2 Study of MK-1045, A Novel CD19 × CD3 T-Cell Engager, in Adult Participants With Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia

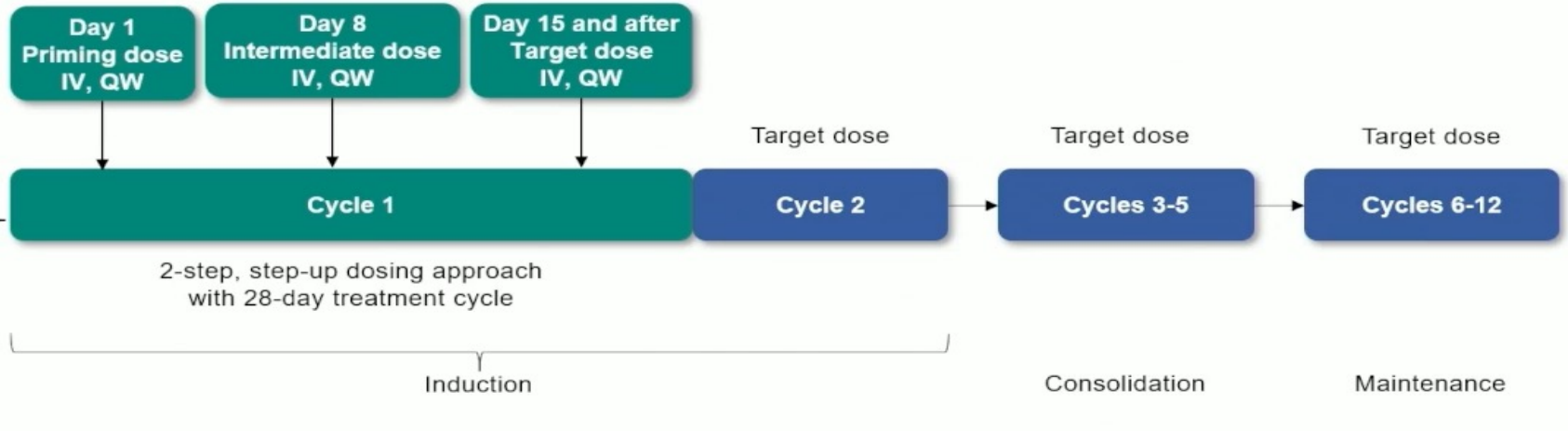
Ying Wang[1]; Qingsong Yin[2]; Jinhai Ren[3]; Hongsheng Zhou[4]; Tiejun Gong[5]; Feng Zhu[6]; Xi Zhang[7]; Qin Wen[7]; Heng Mei[8]; Wei Huang[9]; Zhenghong Chen[10]; Bhargava Kandala[11]; Jingxia Chen[12]; Jianxiang Wang[1]

[1]Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China; [2]The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China; [3]The Second Hospital of HeBei Medical University, Shijiazhuang, China; [4]Nanfang Hospital, Southern Medical University, Guangzhou, China; [5]Institute of Harbin Hematology & Oncology, The First Hospital of Harbin, Harbin, China; [6]The Affiliated Hospital of Xuzhou Medical University, Xuzhou, China; [7]Medical Center of Hematology, Xinqiao Hospital of Army University, Chongqing, China; [8]Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [9]Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [10]MSD China, Beijing, China; [11]Merck & Co., Inc., Rahway, NJ, USA; [12]MSD China, Shanghai, China

Open-Label, Multicenter, Phase 1b/2 Study Study Design (NCT05579132)

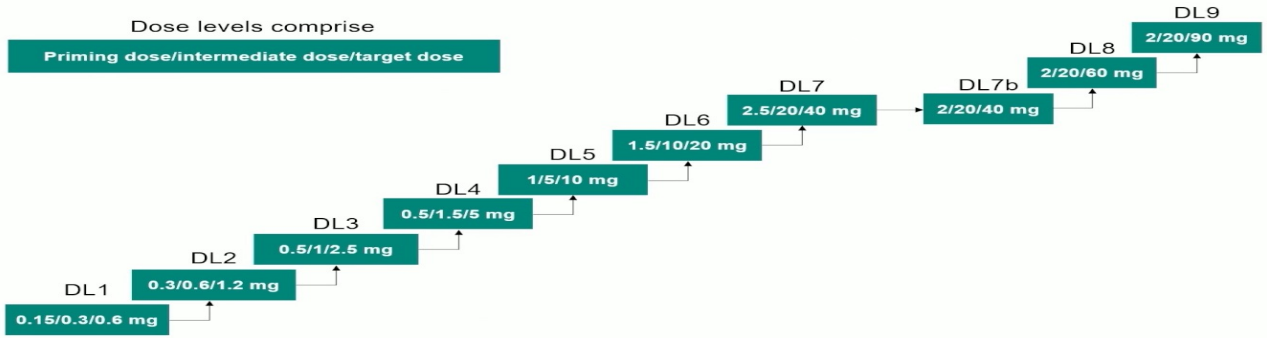
Key Eligibility Criteria

- R/R B-ALL with >5% bone marrow blasts
- Refractory to primary induction therapy or salvage therapy
- Relapse within 12 months after first remission
- Second or later relapse
- Ph+ participants had to have received treatment with ≥2 TKIs, or have T315I mutation, in addition to the above criteria
- ECOG PS 0-2



No treatment-free interval between cycle 1 and 2. After cycle 2, 2-week treatment-free interval between each following cycle

Dose Escalation



Wang Y, et al. Abs N 647

75 patients treated
2/20/60 mg dose CR: 75%
2/20/90 mg: 92%
CRS gr ≥ 3: 3%
ICANS gr ≥ 3: 0

Publication Number: 31

Abstract Title : Genomic determinants of treatment outcome and identification of a new genomic subset of adult acute lymphoblastic leukemia from the ECOG-ACRIN E1910 randomized phase III trial

Publication Number: 440

Abstract Title : Randomized comparison of ponatinib versus imatinib in combination with chemotherapy in patients 55 years of age and older with newly diagnosed ph+ ALL: Molecular response and initial outcome analysis of the EWALL PH03 Study

Publication Number: 444

Abstract Title : Inotuzumab ozogamicin then blinatumomab for older adults with newly diagnosed, ph-negative, CD22-positive, B-cell acute lymphoblastic leukemia: Extended follow-up of alliance for clinical trials in oncology A041703 cohort 1 reveals durable remission and survival

Publication Number: 3345

Abstract Title : Safety and efficacy of surovatamig (AZD0486) in adolescent and adult patients with relapsed or refractory (R/R) B-cell acute lymphoblastic leukemia (B-ALL): Updated Results from the Phase 1/2 SYRUS study


Thank You!
alt

Randomised Comparison of Ponatinib Versus Imatinib in Combination with Chemotherapy in Patients 55 Years of Age and Older with Newly Diagnosed Ph+ ALL: Molecular Response and Initial Outcome Analysis of the EWALL PH03 Study

Primary Endpoint

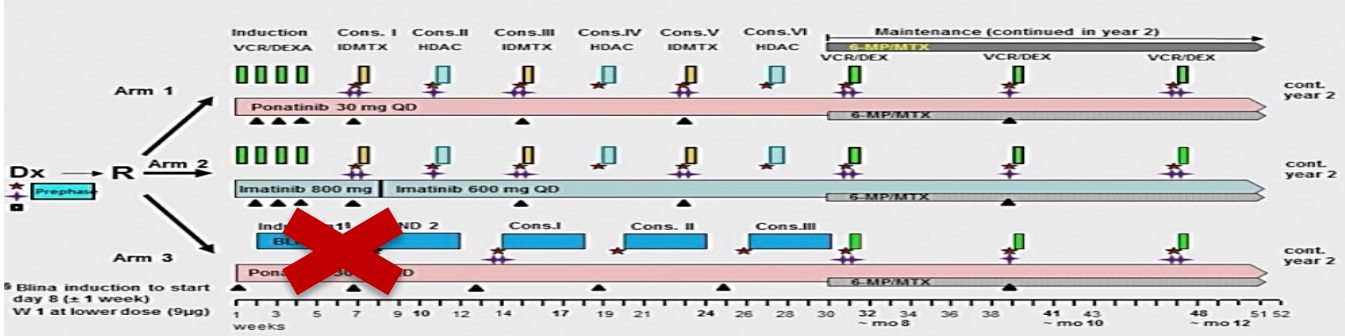
To compare the **molecular response** to **ponatinib** and **imatinib** in combination with EWALL induction and consolidation chemotherapy

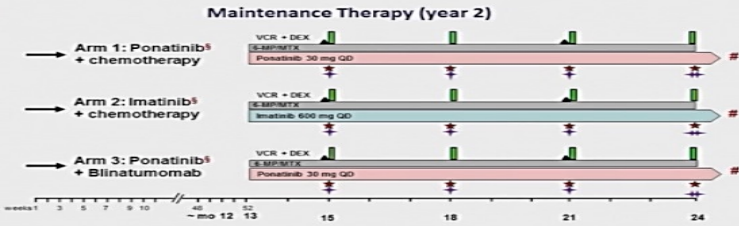
Defined by a BCR::ABL1 transcript ratio ≤ **0.01%** **(MR4)** after consolidation 2

Key secondary Endpoint

To compare the **E**vent **F**ree **S**urvival with **ponatinib** and **imatinib** in combination with EWALL induction and consolidation chemotherapy

Patients who discontinue study treatment because of allogeneic (HSCT) are censored





§ Maintenance with the same TKI as per initial randomisation
# To be continued indefinitively unless criteria for molecular relapse are met
PB: BCR-ABL1/ABL1 (RT-PCR)
BM: BCR-ABL1/ABL1 (RT-PCR)
BM: BCR-ABL1/ABL1 (RT-PCR) and Ig gene rearrangement (PCR)
TKD mutation testing if BCR-ABL1 positive
Intrathecal MTX
Intrathecal triple therapy

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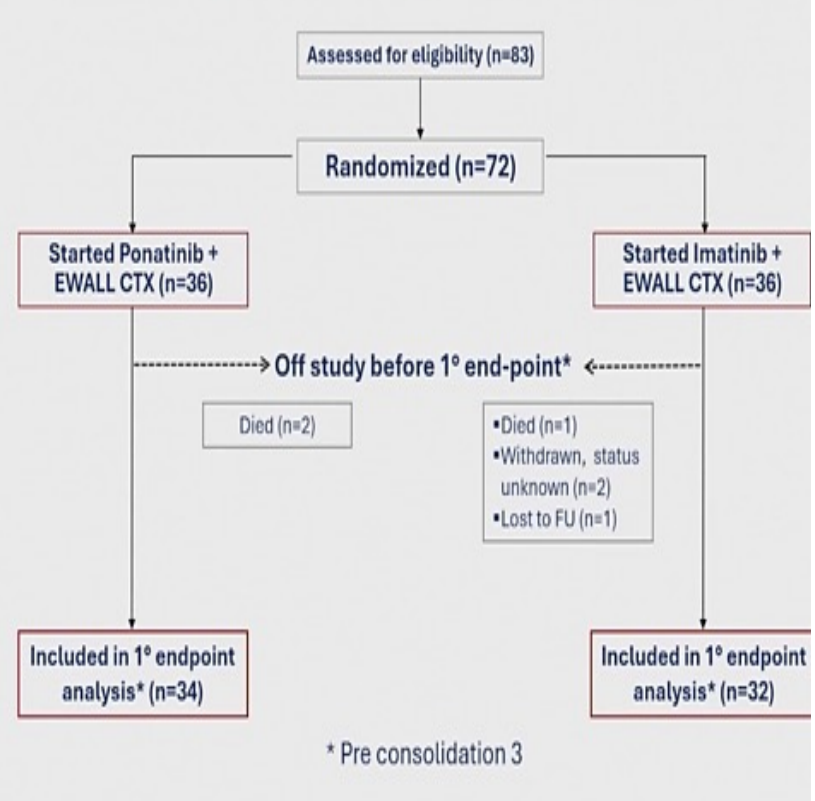
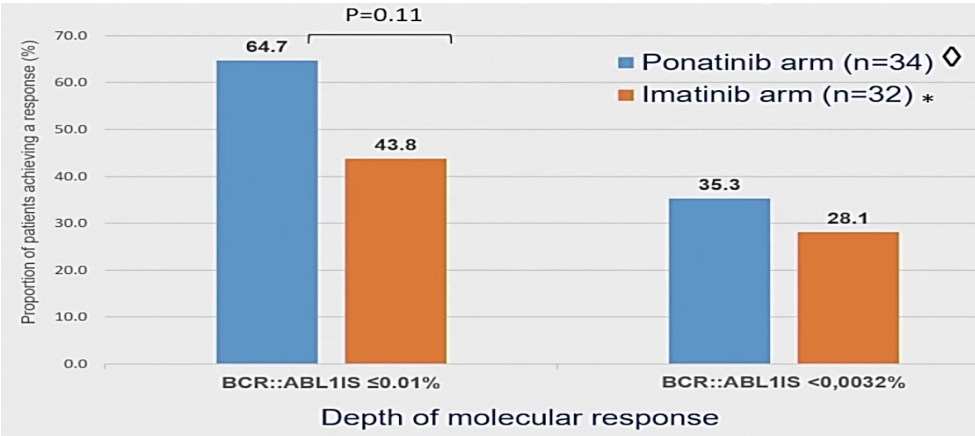
Disposition



Responses

	End of induction phase 1 n (%)		After consolidation cycle 2* n (%)	
Response	Ponatinib arm (n=36)	Imatinib arm (n=36)	Ponatinib arm (n=36)	Imatinib arm (n=36)
Evaluable (n)	34	34	32	29
CHR	32 (94.1)	31 (91.2)	32 (100)	27 (93.1)
Partial	0 (0)	1 (2.9)	0 (0)	0 (0)
Progression	1 (2.9)	0 (0)	0 (0)	1 (3.4)
Relapse	0 (0)	0 (0)	0 (0)	0 (0)



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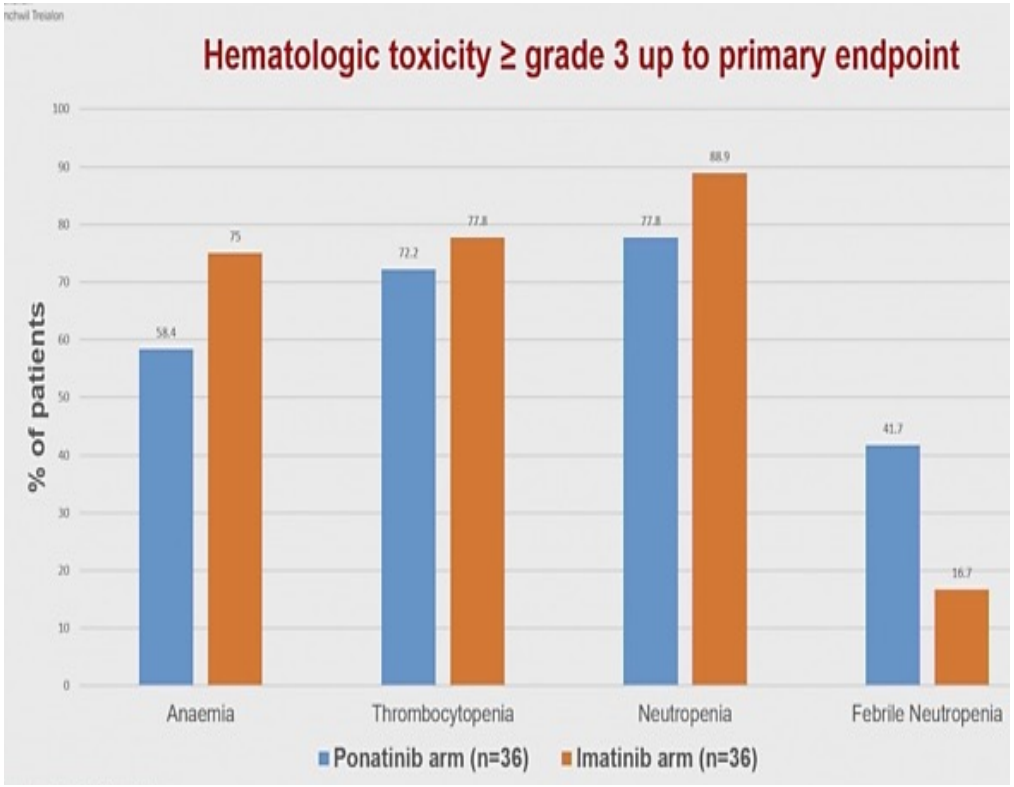
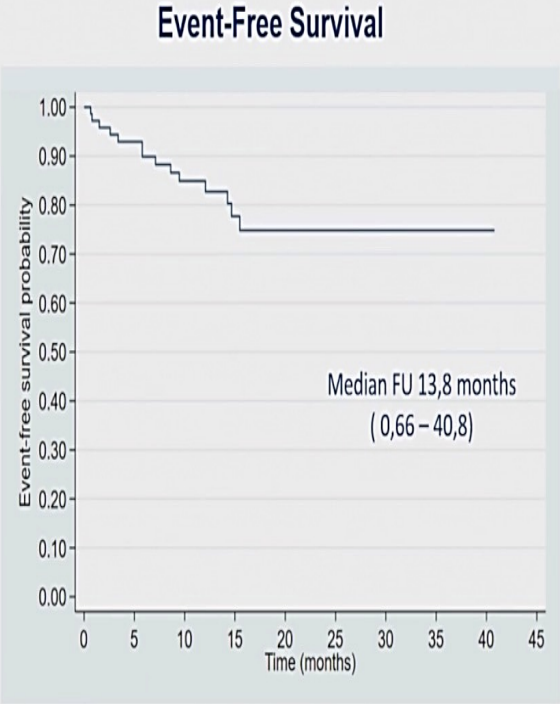
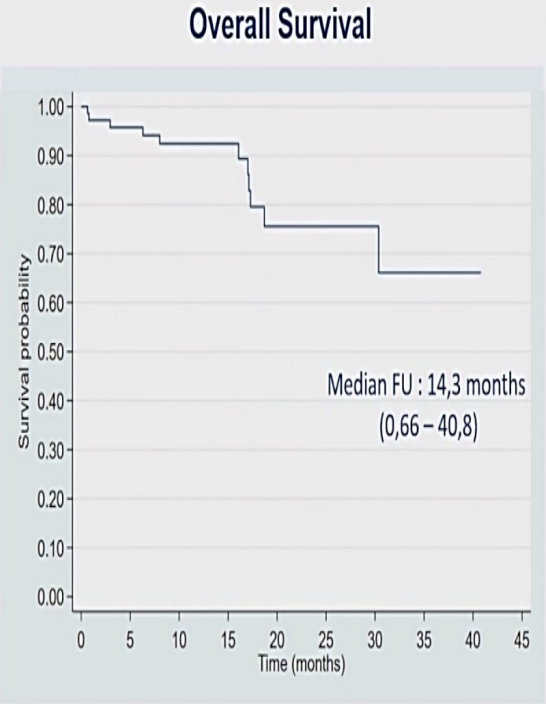
Toxicity



Survival





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Canolfan Ymchwil Treialon

Conclusion

- In the context of the EWALL chemotherapy backbone, PON induces a non-significantly higher molecular response rate than IM in older patients with de novo Ph+ALL
- The safety profile of PON was consistent with known AEs, with no increase in the rate of withdrawal from study treatment compared to IM
- Overall safety and tolerability of ponatinib and imatinib were equivalent
- Combining PON or IM with mild induction and intensive consolidation chemotherapy was applicable with low toxicity even in an older population
- `CNS-active´ ID-MTX and HDAC consolidation cycles may have contributed to the absence of CNS relapses to date
- Assessing the impact on survival will require longer follow-up

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